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TITLE: **Treatment of Pain and Autonomic Dysreflexia in Spinal Cord Injury with Deep Brain Stimulation**

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CONTRACTING ORGANIZATION: **University of Miami School of Medicine Miami, Florida 33136**

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14. ABSTRACT

This project aims to study electrical deep brain stimulation as a method for treating pain and autonomic dysflexia in patients with chronic spinal cord injury. It consists of a collaboration between the University of Miami and the Miami Veterans Administration Hospital. It involves an invasive surgical procedure performed at the University of Miami Hospital. All 8 subjects will be patients of the spinal cord clinic of the Miami VAH. Testing for pain and other symptoms of spinal cord injury will be done at both sites. Since this project entails critical invasive surgery and pain measurement, the first year was taken up with obtaining regulatory approval consecutively from the FDA (an investigative device exemption) and from the IRBs of the two sites. These processes involved considerable back-and-forth discussion and revision of protocols. All approvals have now been obtained: FDA conditional approval 20 December 2012, amended 10 May 2013, University of Miami IRB 16 July 2012, Miami VAH IRB 18 September 2013. Recruitment of subjects is now planned to begin in December 2013. We anticipate completing all proposed procedures and testing within the 3 years of the funded grant.

15. SUBJECT TERMS none provided

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Introduction

Deep brain stimulation (DBS) has been used for several decades to treat drug-refractory pain of various types. A major stimulation site for this is the periaqueductal/ periventricular gray region (PAG/PVG). Chronic pain severely affects the quality of life of many spinal cord injury (SCI) patients. Autonomic dysreflexia (AD) is another major problem in SCI, manifested as hypertension and other sympathetic over-activity elicited by noxious cutaneous or visceral stimuli below the injury level. Our preclinical studies on rats have shown that PAG stimulation, given for one to a few weeks, can permanently reverse AD and some motor deficits of SCI. We propose testing of PAG/PVG stimulation for acute palliation and long-term remediation of these problems in a human phase I study of safety and efficacy. All subjects will have moderately severe chronic neuropathic pain due to SCI, with concomitant AD, and will be recruited from the Spinal Cord Injury Service of the Miami Veterans Administration Medical Center. Eight patients will be studied. We shall test whether DBS in the PAG/PVG region of SCI patients is safe, at a level compared to other current uses of DBS and to other (drug) treatments for pain and AD in SCI. We will furthermore determine whether acute DBS in the PAG/PVG lowers ongoing chronic pain severity caused by longstanding SCI. Finally, we will explore how prolonged PAG/PVG stimulation over 10 months cumulatively affects the sensory, motor and autonomic deficits of SCI, including the frequency of AD episodes. If DBS in the PAG/PVG proves successful in ameliorating the immediate pain and autonomic deficits of SCI, or achieves partial recovery in the longer term, a new treatment for such individuals, whose lives are severely degraded by these symptoms, will become available. It will offer veterans and active service members with debilitating SCI the possibility of return to a productive and enjoyable life, including work activities that were not previously feasible.

Body

Investigators

1. Jonathan R. Jagid, MD. Associate Professor of Neurological Surgery, UMMSM

2. Bruno V. Gallo. MD. Assistant Professor of Neurology, Director of Intraoperative Neurophysiology, UMMSM. Co-investigator

3. Ian D. Hentall, Ph.D. Research Associate Professor, the Miami Project to Cure Paralysis, UMMSM. Co-investigator

4. Alberto Martinez-Arizala. MD. Associate Professor of Clinical Neurology, Chief of the Spinal Cord Injury Service (Miami VA)

5. Eva Widerström-Noga, PhD. Research Associate Professor, the Miami Project to Cure Paralysis, UMMSM. Co-investigator

Consultants: Medical monitors

1. M. Ross Bullock, MD. Professor of Neurological Surgery, Clinical Director, Neurotrauma, UMMSM

2. Diana D. Cardenas, MD, MHA. Professor and Chair, Department of Rehabilitation Medicine, UMMSM

Human subjects

Total number: 8. Recruited at Miami VA; surgery at University of Miami Hospital; longitudinal measurement of pain other SCI symptoms at Miami VAH.

Statement of work from grant proposal.

Task 1. Regulatory review and approval processes for studies of human subjects

1a Obtain manufacturer cross-reference authorization letter before 04/12

OUTCOME. Right-of reference letter obtained from Medtronic, Inc., 11 July, 2012

1b Obtain IDE from FDA before 06/12

OUTCOME. Conditional approval for IDE granted on 27 September 2012, amendments partly approved on 20 December 2012, amendments approved with no conditions remaining on 10 May 2013.

1c Obtain CDMRP approval for human subject use months 1-2

OUTCOME. The revised research consent forms and associated study documents received at the U.S. Army Medical Research and Materiel Command (USAMRMC), Office of Research Protections (ORP) Human Research Protection Office (HRPO) on 23 July 2013. All documents received have been reviewed and found to comply with applicable Federal, DOD, and USAMRMC human subject's protection regulations. To date, all requests for additional information and revisions to the informed consent forms and recruitment materials have been satisfied.

1d Obtain local (Miami VA and UMMSM) IRB approval months 3-4

OUTCOME. Approval of Human Subject protocols obtained from University of Miami IRB 10 June 2013. Approval of Human Subject protocols obtained from Miami Veterans Administration Hospital IRB on August 29 2013, with amendments approved to align it with the University of Miami protocol on 18 September 2013.

Task 2. Setting up project

2a Review all forms; create standard operating procedures (SOPs) months 1-4

OUTCOME. All necessary forms for screening, enrollment, informed consent, training, inventory, adverse event reporting, protocol deviation and clinical testing have been created. SOPs were created in IRB protocols.

2b Ensure that all personnel are aware of SOPs months 3-5.

OUTCOME. Personnel have been informed of SOPs and continue to receive information at bi-weekly meetings.

2c Set up accounts and coordinate purchasing with local site administrators months 3-5

OUTCOME. Accounts were set up in timely manner after award disbursement.

Task 3. Recruitment of subjects

NOT STARTED.

3a Place announcements: local SCI community newsletters, websites months 5-18

3b Inform patients in Miami VA SCI clinics months 5-18

Task 4. Enrollment of first subject

NOT STARTED.

4a Explain study and obtain stage-1 consent month 6

4b Screen and obtain stage-2 consent month 7

Task 5. Pre-surgery testing, screening and consenting for first subject

NOT STARTED.

5a Conduct 1st comprehensive testing months 8

5b Conduct telephone interview to assess symptoms months 8-9

5c Conduct 2nd comprehensive testing, 4 weeks from 1st month 9

5c Obtain stage-3 consent and screen for surgery contraindication month 9

Task 6. Surgery for first subject

NOT STARTED.

6a Admission to UM Hospital month 9

6b Brain imaging for neurosurgical targeting month 9

6c Implant leads in cranium month 9

6d Hospital discharge, 1 week after lead implantation month 9

6e Internalize generator, 1 week after lead implantation; test effects month 9 or 10

Task 7. Post-surgery testing for first subject

NOT STARTED.

7a Activate stimulator for continuous stimulation month11

7b Conduct 3rd comprehensive testing month11

7c Telephone report of symptoms, weekly, 3 between each monthly visit months 11-20

7d Assess pain and other symptoms monthly; reprogram stimulator months 11-20

7e Conduct 4th comprehensive testing month 15

7f Conduct 5th comprehensive testing; plus study exit interview month 20

Task 8. Procedure on subjects after the first, following template of Tasks 4-7

NOT STARTED.

8a Subject #2 months 9-21

8b Subject #3 months 10-22

8c Subject #4 months 11-23
8d Medical monitors routine review of first 4 subjects month 13
8e Subject #5 months 14-26
8f Subject #6 months 15-27
8g Subject #7 months 16-28
8h Subject #8 months 17-29
8i Medical monitors routine review of last 4 subjects month 18

Task 9. Regulatory reporting
OUTCOME. Annual and 3-monthly reporting to listed agencies is on schedule.
9a FDA annual report months 12, 24, 36
9b Local IRBs annual reports months 12, 24, 36
9c Report to Manufacturer months 15, 30
9d Reporting to CDMRP months 12, 24, 36

Task 10. Publication and Dissemination of Findings
NOT STARTED.
Analysis, months 20-36
Attend National Neurotrauma Society annual meeting, month 12
Present poster or talk on current results at National Neurotrauma Society meeting, month 24
Present poster or talk, current results, at meting of American Society for Stereotaxic and Functional Neurosurgery, month 24
Prepare article and submit findings to clinical pain journal, months 30-36
Prepare article and submit findings to neurosurgery journal months 30-36
Prepare article and submit findings to rehabilitation journal, months 30-36s

Key Research Accomplishments

Research has not yet begun. Recruitment is anticipated to start in December 2013.

Reportable Outcomes

Manuscripts, abstracts, presentations: none.
Licenses applied for and/or issued: none.
Degrees obtained that are supported by this award: none.
Development of cell lines, tissue or serum repositories: none.
Informatics such as databases and animal models, etc.: none.
Funding applied for based on work supported by this award none
Employment or research opportunities based on experience/training supported: none.

Conclusion

The first year of this award was occupied in obtaining regulatory approvals. This process is now essentially complete and recruitment is planned to begin in December 2013.

References

None.

Appendices

None.